AUSTRALIAN PRODUCT INFORMATION – DBL™ ACETYLCYSTEINE INJECTION CONCENTRATE (Acetylcysteine)

1. NAME OF THE MEDICINE

Acetylcysteine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 200 milligrams/mL of acetylcysteine as well as sodium hydroxide, disodium edetate and water for injections.

DBL Acetylcysteine Injection Concentrate is a clear, colourless, sterile, pyrogen free aqueous solution of acetylcysteine (N-acetyl-mercapto-alanine) with a pH of approximately 7.0. It is soluble in water and alcohol and practically insoluble in chloroform, dichloromethane and ether.

For the full list of excipients, see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

DBL Acetylcysteine is a concentrated injection for intravenous use.

Acetylcysteine is a white, crystalline powder with a slight acetic odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

As an antidote for paracetamol poisoning: DBL Acetylcysteine Injection Concentrate is indicated in the treatment of paracetamol overdose to protect against hepatotoxicity.

4.2 Dose and Method of Administration

Dosage

DBL Acetylcysteine Injection Concentrate is infused in two intravenous infusions containing different doses.

Adults (age ≥14 years)

INITIAL INFUSION: An initial dose of 200 milligrams/kg (maximum 22 g) of acetylcysteine diluted in 500 mL of 5% glucose or 0.9% sodium chloride and infused intravenously over 4 hours.

SECOND INFUSION*: The initial infusion is followed by a continuous intravenous infusion of 100 milligrams/kg (maximum 11 g) of acetylcysteine in 1000 mL of 5% glucose or 0.9% sodium chloride over 16 hours.

- *If the initial serum paracetamol concentration was more than double the nomogram line (refer to Figure 1) following an acute ingestion of paracetamol, increase acetylcysteine dose to 200 milligrams/kg (maximum 22 g) diluted in 1000 mL of 5% glucose or 0.9% sodium chloride intravenously, over 16 hours.

Children (age <14 years)

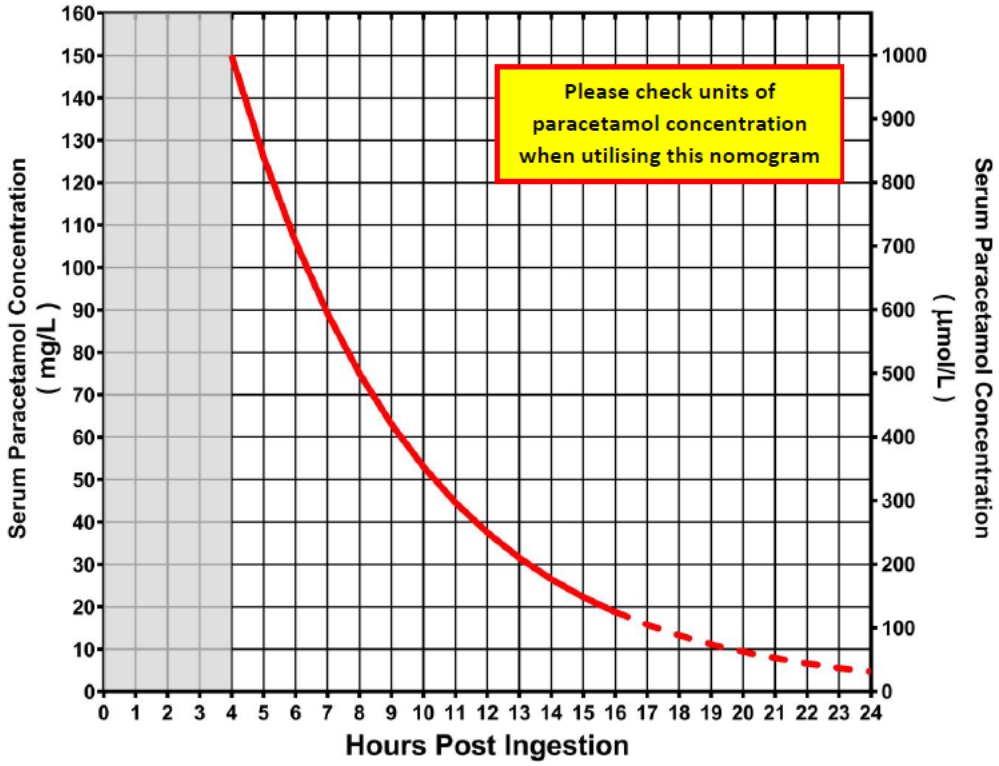
Children should be treated with the same doses (milligrams/kg) and regimens as adults. However the volume of intravenous fluid should be modified to take into account age and weight, as fluid overload is a potential danger in children.

INITIAL INFUSION: An initial dose of 200 milligrams/kg (maximum 22 g) of acetylcysteine diluted in 7 mL/kg up to 500 mL of 5% glucose or 0.9% sodium chloride and infused intravenously over 4 hours.

SECOND INFUSION*: The initial infusion is followed by a continuous intravenous infusion of 100 milligrams/kg (maximum 11 g) of acetylcysteine in 14 mL/kg up to 1000 mL of 5% glucose or 0.9% sodium chloride over 16 hours.

- *If the initial serum paracetamol concentration was more than double the nomogram line (refer to Figure 1) following an acute ingestion of paracetamol, increase acetylcysteine dose to 200 milligrams/kg (maximum 22 g) diluted in 14 mL/kg up to 1000 mL of 5% glucose or 0.9% sodium chloride intravenously, over 16 hours.

Figure 1. Paracetamol Treatment Nomogram (Rumack-Matthew Nomogram)



*Note: µmol/L = micromol/L = nmol/mL

DBL Acetylcysteine Injection Concentrate intravenous infusion dosage guide

DBL Acetylcysteine Injection Concentrate is supplied in ampoules containing 10 mL of 200 milligrams/mL acetylcysteine for intravenous administration.

Since DBL Acetylcysteine Injection Concentrate does not contain an antimicrobial preservative, use each ampoule in one patient on one occasion only and discard any residue.

The following tables are intended as a guide on the dose (g) and volume (mL) of DBL Acetylcysteine Injection Concentrate 200 milligrams/mL that is required to be added to 5% glucose or 0.9% sodium chloride to prepare the initial and second infusion solutions. In order to use these tables, the patient's weight in kilograms should be determined.

Adults (age ≥14 years)

For adults (age ≥14 years), dosing should be based on actual body weight rounded to the nearest 10 kg, with a ceiling weight of 110 kg.

Table 1. Dose and Volume of Acetylcysteine to be Used for Each Infusion, in Adults

PATIENT'S BODY WEIGHT (kg)	**BAG 1: INITIAL INFUSION** (200 milligrams/kg (maximum 22 g) of acetylcysteine to be added to 500 mL of 5% glucose or 0.9% sodium chloride)		**BAG 2: SECOND INFUSION*** (100 milligrams/kg (maximum 11 g) of acetylcysteine to be added to 1000 mL of 5% glucose or 0.9% sodium chloride)	
	Dose (g) of Acetylcysteine	Volume (mL) of Acetylcysteine	Dose (g) of Acetylcysteine	Volume (mL) of Acetylcysteine
50	10 g	50 mL	5 g	25 mL
60	12 g	60 mL	6 g	30 mL
70	14 g	70 mL	7 g	35 mL
80	16 g	80 mL	8 g	40 mL
90	18 g	90 mL	9 g	45 mL
100	20 g	100 mL	10 g	50 mL
110 **(maximum dose)**	22 g	110 mL	11 g	55 mL

* Note: If the serum paracetamol concentration was more than double the nomogram line, increase acetylcysteine dose to 200 milligrams/kg.

Children (age <14 years)

For children (age <14 years), use actual body weight to calculate dose of acetylcysteine and volume of diluent.

Table 2. Dose and Volume of Acetylcysteine & Volume of Diluent to be Used for Each Infusion, in Children

PATIENT'S BODY WEIGHT (kg)# (examples)	**BAG 1: INITIAL INFUSION** (200 milligrams/kg (maximum 22 g) of acetylcysteine to be added to 7 mL/kg up to 500 mL of 5% glucose or 0.9% sodium chloride)			**BAG 2: SECOND INFUSION*** (100 milligrams/kg (maximum 11 g) of acetylcysteine to be added to 14 mL/kg up to 1000 mL of 5% glucose or 0.9% sodium chloride)		
	Dose (g) of Acetylcysteine	Volume (mL) of Acetylcysteine	Volume (mL) of Diluent	Dose (g) of Acetylcysteine	Volume (mL) of Acetylcysteine	Volume (mL) of Diluent
15	3 g	15 mL	105 mL	1.5 g	7.5 mL	210 mL
20	4 g	20 mL	140 mL	2 g	10 mL	280 mL
25	5 g	25 mL	175 mL	2.5 g	12.5 mL	350 mL

Use actual body weight.

* Note: If the serum paracetamol concentration was more than double the nomogram line, increase acetylcysteine dose to 200 milligrams/kg

Method of Administration

To be most effective in protecting against liver damage, therapy with DBL Acetylcysteine Injection Concentrate should be started within 8 hours of paracetamol ingestion.

Management of Paracetamol Overdosage with Acetylcysteine

The paracetamol treatment nomogram is used to decide whether to start or continue acetylcysteine infusion. The dosing depends on the time since paracetamol ingestion, formulation of paracetamol, dose ingested, serum paracetamol concentration (early), and presence of clinical and laboratory features suggesting acute liver injury.

It should be noted that, after an ingestion of a potentially fatal dose of paracetamol, the patient may appear relatively well initially and may even continue normal activities for a day or two before the onset of hepatic failure. Hepatic damage is more likely to occur with a lower dosage of paracetamol in patients who have a history of chronic alcohol or enzyme-inducing drug ingestion (e.g. isoniazid, rifampicin, anticonvulsants including carbamazepine, phenytoin, phenobarbitone, primidone, sodium valproate).

Patients are notoriously unreliable as to the amount ingested and the time of ingestion. Hepatic necrosis is preventable if treatment can be instituted within 8 hours of ingestion.

Note: Liver damage may not be clinically or biochemically apparent for up to 24 hours after ingestion.

Hepatic necrosis has been seen with 6 grams of paracetamol, and death with 15 grams.

The following A-C sections are applicable to both adults and children, for both solid and liquid paracetamol ingestion.

A. Acute Ingestion of Immediate-Release Paracetamol

- In patients who present within 8 hours after an acute overdose, with a serum paracetamol concentration on or over the nomogram line, commence acetylcysteine infusion.*

- In patients who present between 8 to 24 hours after an acute overdose, commence acetylcysteine infusion immediately. Measure serum paracetamol concentration and ALT. For patients who have serum paracetamol concentration on or over the nomogram line and/or ALT >50 U/L, continue the rest of the treatment (otherwise no further treatment is required).*

** For patients who have serum paracetamol concentration double the nomogram line, complete acetylcysteine infusion with double dose of the second bag (200 milligrams/kg over 16 hours).*

- In patients who present more than 24 hours after an acute overdose, commence acetylcysteine infusion immediately. Measure serum paracetamol concentration and ALT. If serum paracetamol concentration is ≥10 milligrams/L (66 μmol/L) and/or ALT >50 U/L, continue the rest of the treatment (otherwise no further treatment required).

- In patients whose time of ingestion is not known, follow the advice above for between 8 to 24 hours after an acute overdose, commence acetylcysteine immediately. Measure

serum paracetamol concentration and ALT. If the serum paracetamol concentration is ≥10 milligrams/L (66 μmol/L) and/or the ALT is >50 U/L, continue the rest of the treatment (otherwise no further treatment required).

Two hours before the completion of acetylcysteine infusion, ALT measurement should be repeated in all patients. For those with an initial serum paracetamol concentration double the nomogram line, a serum paracetamol concentration should also be repeated. Acetylcysteine treatment should be continued if the serum paracetamol concentration is >10 milligrams/L (66 μmol/L), or ALT is elevated (>50 U/L) and increasing (if baseline ALT >50 U/L).

B. Acute Ingestion of Modified-Release (MR) Paracetamol

- In patients who ingested MR paracetamol dose of <10 grams AND <200 milligrams/kg, measure 2 serum paracetamol concentrations at least 4 hours post-ingestion and 4 hours apart. If either serum paracetamol concentration is over the nomogram treatment line, commence acetylcysteine infusion.*

- In patients who ingested MR paracetamol dose of ≥10 grams or ≥200 milligrams/kg (whichever is less) and present more than 4 hours post-ingestion, commence acetylcysteine infusion immediately.

    - If dose ingested is ≥30 grams or ≥500 milligrams/kg (whichever is less), complete acetylcysteine infusion with double dose of the second bag (200 milligrams/kg over 16 hours).

    - If dose ingested is NOT ≥30 grams or NOT ≥500 milligrams/kg, measure 2 serum paracetamol concentrations at least 4 hours post-ingestion and 4 hours apart, and if either serum paracetamol concentration is more than double the nomogram treatment line, acetylcysteine treatment should be continued.*

** For patients with either of the two serum paracetamol concentration more than double the nomogram line, complete acetylcysteine infusion with double dose of the second bag (200 milligrams/kg over 16 hours).*

Measure serum paracetamol concentration and ALT for all patients before ceasing acetylcysteine infusion. Acetylcysteine treatment should be continued if serum paracetamol concentration is >10 milligrams/L (66 μmol/L), or ALT is elevated (>50 U/L) and increasing (if baseline ALT >50 U/L).

C. Repeated Supratherapeutic Ingestion (RSTI) of Paracetamol

Patients who ingest excessive paracetamol for a therapeutic purpose (e.g. pain, viral illness) or ingest therapeutic doses of paracetamol and have symptoms of acute liver injury (e.g. abdominal pain, nausea and vomiting) are managed as RSTI. If the ingestion is deliberate/intentional they should be managed as per acute intentional ingestion.

- In patients who ingested paracetamol dose of ≥10 grams or ≥200 milligrams/kg (whichever is less) over a single 24 hour period, and have an ALT ≥50 U/L or serum paracetamol concentration ≥20 milligrams/L (132 μmol/L), commence acetylcysteine infusion.

- In patients who ingested paracetamol dose of ≥12 grams or ≥300 milligrams/kg (whichever is less) over a single 48 hour period, and have an ALT ≥50 U/L or serum

paracetamol concentration ≥20 milligrams/L (132 μmol/L), commence acetylcysteine infusion.

- In patients who ingested a daily therapeutic dose per day for more than 48 hours in those who also have abdominal pain or nausea or vomiting, and have an ALT ≥50 U/L or serum paracetamol concentration ≥20 milligrams/L (132 μmol/L), commence acetylcysteine infusion.

Repeat serum paracetamol concentration and ALT, 8 hours after the previous concentration sampling. If ALT ≥50 U/L or serum paracetamol concentration ≥10 milligrams/L (66 μmol/L), continue acetylcysteine infusion and check ALT at 12 hourly intervals.

D. Paediatric (<6 years) liquid paracetamol ingestion

In children less than 6 years of age, where ingestion of greater than 200 milligrams/kg of liquid paracetamol is suspected, a serum paracetamol concentration should be measured as least 2 hours post-ingestion. If the 2-hour post-ingestion serum paracetamol concentration is greater than 150 milligrams/L (1000 μmol/L), this should be repeated 4 hours post-ingestion and acetylcysteine commenced if this is ≥150 milligrams/L (1000 μmol/L). Further, for those children who present later than 4 hours post-ingestion or in children older than 6 years of age, treatment is as per the adult acute paracetamol exposure guideline.

E. General Management

DBL Acetylcysteine Injection Concentrate should be administered if appropriate (see above). DBL Acetylcysteine Injection Concentrate should be diluted in 5% glucose or 0.9% sodium chloride solution, and administered by intravenous infusion. Nausea should be treated.

Measurements of plasma liver enzymes and bilirubin levels, and coagulation studies, should be performed as soon as possible after admission.

Daily liver function tests, and measurements of plasma urea, electrolytes, glucose, blood gases, haemoglobin levels, white blood cell counts, platelets and prothrombin time should be made. An ECG should also be performed. Patients should be monitored for coagulation disorders, hepatic encephalopathy, renal failure and cardiac toxicity (minor ST changes are common). There is usually a mild metabolic acidosis. Hepatic encephalopathy is likely if bilirubin is above 60 millimoles per litre on days 3 to 5, or if the prothrombin time is prolonged.

If ongoing acetylcysteine treatment is required, continue at the rate of the second infusion (e.g. 100 milligrams/kg over 16 hours). Higher ongoing infusion rates (e.g. 200 milligrams/kg over 16 hours) may be required for massive paracetamol ingestions and a clinical toxicologist should be consulted.

4.3 Contraindications

DBL Acetylcysteine Injection Concentrate is contraindicated in patients with hypersensitivity or previous anaphylactic reaction to acetylcysteine or any component of the preparation.

4.4 Special Warnings and Precautions for Use

DBL Acetylcysteine Injection Concentrate should be used with caution in asthma or where there is a history of bronchospasm. It should also be used with caution with patients with a past

history of oesophageal varices and peptic ulceration (acetylcysteine induced vomiting may increase the risk of haemorrhage).

Acetylcysteine is not compatible with rubber and some metals, particularly, iron, copper and nickel. DBL Acetylcysteine Injection Concentrate can be used satisfactorily with silicone rubber and plastic.

Patients with body weight less than 40 kg

For patients weighing less than 40 kg, adjustment of total volume is recommended when administering acetylcysteine, to minimise the risk of hyponatraemia, seizure, and death (see Section 4.2 Dose and Method of Administration).

Patients on fluid restriction

For patients on fluid restriction, adjustment of total volume is recommended when administering acetylcysteine, to minimise the risk of hyponatraemia, seizure, and death.

Use in hepatic impairment

Caution should be taken when administering acetylcysteine in patients with hepatic failure, since there is little data relating to the effects of acetylcysteine in impaired hepatic function. The decision to administer should be passed on a risk/benefit assessment for the individual subject.

In the presence of hepatic failure due to paracetamol overdose the degree of existing liver damage and the possible risk associated with the administration of acetylcysteine should be considered.

Use in renal impairment

Caution should be taken when administering acetylcysteine in patients with renal failure, since there is little data relating to the effects of acetylcysteine in impaired renal function. The decision to administer should be passed on a risk/benefit assessment for the individual subject.

Use in the elderly

There are no adequate or well controlled studies in elderly patients. For this reason, the safety and effectiveness of DBL Acetylcysteine Injection Concentrate in the elderly has not been established.

Paediatric use

The safety and effectiveness of DBL Acetylcysteine Injection Concentrate in children have not been established. There is some limited clinical data in the use of acetylcysteine injection in children. (See section 5.1 Pharmacodynamic Properties – Clinical Trials).

No paediatric specific adverse effects have been documented.

Use of DBL Acetylcysteine Injection Concentrate in paediatric patients is based on clinical practice (see Section 4.2 Dose and Method of Administration).

Effects on laboratory tests

Acetylcysteine may cause a false-positive reaction with reagent dipstick tests for urinary ketones.

4.5 Interactions with Other Medicines and Other Forms of Interactions

No information is available on the interaction of acetylcysteine with other medicines.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

There was evidence of effects on fertility in male rats given acetylcysteine at doses up to 60% of the maximum clinical dose, on a body surface area basis. No effects were observed at doses 15% the maximum clinical dose, on a body surface area basis.

Use in pregnancy – Category B2

Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

There was no evidence of teratogenicity in limited studies in rats and rabbits following administration of acetylcysteine during the period of gestation at doses up to 1.2 times the maximum clinical dose, on a body surface area basis.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage. There are no well controlled studies in pregnant women but experience does not include any positive evidence of adverse effects to the foetus.

Use in lactation

There was no evidence of adverse effects in a limited study in rats following administration of acetylcysteine during late gestation and lactation at 60% of the maximum clinical dose, on a body surface area basis. It is not known whether acetylcysteine and/or its metabolites are excreted in milk. There are no data on the use of acetylcysteine in lactating women and therefore breastfeeding is not recommended during treatment.

4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse Effects (Undesirable Effects)

Intravenous administration of acetylcysteine, especially in the large doses needed to treat paracetamol overdose, may result in nausea, vomiting and other gastrointestinal symptoms. Hypersensitivity reactions have been reported following intravenous administration of acetylcysteine. Bronchospasm may occur in conjunction with a generalised anaphylactoid reaction. The symptoms of the anaphylactic like reaction to acetylcysteine include airway obstruction (bronchospasm), angioedema, dyspnoea, hypotension**,** shock, tachycardia, urticaria, and injection site reaction (including rash). These reactions occur most commonly either during, or at the end of the period of the loading dose infusion, and may in fact be dose

related. Since these anaphylactic-like reactions usually occur following the loading dose, careful monitoring is recommended.

There have been rare instances of death.

The following adverse effects have been reported:

Blood and lymphatic system disorders: Thrombocytopenia

Immune system disorders: Anaphylactoid reaction

Metabolism and nutrition disorders: Acidosis

Psychiatric disorders: Anxiety

Nervous system disorders: Syncope, generalized seizure

Eye disorders: Blurred vision, eye pain

Cardiac disorders: Cyanosis, tachycardia, bradycardia, cardiac arrest, extrasystoles

Vascular disorders: Flushing, hypotension, hypertension, vasodilation

Respiratory, thoracic and mediastinal disorders: Dyspnoea, respiratory arrest, bronchospasm, coughing, stridor

Gastrointestinal disorders: Vomiting, nausea

Hepatobiliary disorders: Deterioration of liver function

Skin and subcutaneous tissue disorders: Angioedema, urticaria, rash (erythematous and maculo-papular), sweating, oedema periorbital

Musculoskeletal and connective tissue disorders: Arthralgia

General disorders and administration site conditions: Malaise, rigors, injection site reaction, chest pain, facial pain, face oedema

Investigations: Raised temperature

Hypokalaemia and ECG changes have been noted in patients with paracetamol poisoning irrespective of the treatment given. Monitoring of plasma potassium concentration is therefore recommended.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Symptoms

Symptoms following overdosage with acetylcysteine have been similar to those of anaphylactoid reactions noted under "**4.8 Adverse effects (Undesirable effects)**", but they may be more severe. Hypotension appears to be especially prominent. There is also a theoretical risk of hepatic encephalopathy.

Treatment

There is no specific treatment. General supportive measures should be carried out.

It has been suggested that generalised reactions to acetylcysteine can be treated with intravenous injection of an antihistamine, and infusion of acetylcysteine should be temporarily stopped but can be restarted at a slower rate without further reaction.

For information on the management of overdose, contact the Poisons Information Centre on

13 11 26.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Paracetamol is metabolised in the liver, mainly by conjugation with glucuronide and sulphate. It is also metabolised by cytochrome P450 to form a reactive, potentially toxic metabolite. This metabolite is normally detoxified by conjugation with hepatic glutathione, to form non-toxic derivatives. In paracetamol overdosage, the glucuronide and sulphate conjugation pathways are saturated, so that more of the toxic metabolite is formed. As hepatic glutathione stores are depleted, this toxic metabolite may bind to hepatocyte proteins, leading to liver cell damage and necrosis. Acetylcysteine is a sulphydryl (SH) group donor, and may protect the liver from damage by restoring depleted hepatic-reduced glutathione levels, or by acting as an alternative substrate for conjugation with, and thus detoxification of, the toxic paracetamol metabolite.

Clinical trials

Observational Study – paediatric patients

An open-label, observational study conducted in the greater Newcastle area, New South Wales, Australia, documented treatment for paediatric patients who presented with a paracetamol overdose during a 16 year period from January 1987 to January 2003. This study was primarily considered a safety study.

Data from 148 paediatric patients, with an age range of 2 months to 15 years (this corresponds to 186 cases) were evaluated. Twenty three (23) out of 148 paediatric patients were given intravenous acetylcysteine treatment on at least one admission. Of these, 14 paediatric patients in the age group 12 to < 16 years (9.5% of the group), received acetylcysteine within 8 hours of ingesting paracetamol on at least one admission. There was a delay of at least 8 hours for 9 paediatric patients in this age group (6.1% of the group). One other paediatric patient in the age

group 2 to < 5 years of age (0.7% of the group), received acetylcysteine with a delay of at least 8 hours on at least one admission.

Of the 23 patients who received intravenous acetylcysteine treatment, 3 patients (13%) experienced an adverse reaction (anaphylactoid reaction, rash and flushing, transient erythema). There were no deaths of paediatric patients. None of the paediatric patients receiving intravenous acetylcysteine developed hepatotoxicity, whilst two patients not receiving intravenous acetylcysteine did develop hepatotoxicity. The number of paediatric patients examined in this study is too small to provide a statistically significant finding for efficacy, however, the results appear to be consistent to those observed in adults.

Safety Study

A randomized, open-label, multi-centre clinical study was conducted in Australia to compare the rates of anaphylactoid reactions between two rates of infusion for the intravenous acetylcysteine loading dose. One hundred and nine subjects were randomized to a 15 minute infusion rate and 71 subjects were randomized to a 60 minute infusion rate. The loading dose was 150 mg/kg, followed by a maintenance dose of 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours. Of the 180 patients examined in this study, 27% were male and 73% were female. Ages ranged from 15 to 83 years, with the mean age being 29.9 years (+13.0).

Within the first 2 hours following intravenous acetylcysteine administration, 17% of all patients developed an anaphylactoid reaction (18% in the 15-minute treatment group; 14% in the 60-minute treatment group) (See section 4.4 Special Warnings and Precautions for Use). A subgroup of 58 subjects (33 in the 15-minute treatment group; 25 in the 60-minute treatment group) was treated within 8 hours of paracetamol ingestion. No hepatotoxicity occurred within this subgroup; however with 95% confidence, the true hepatotoxicity rates could range from 0% to 9% for the 15-minute treatment group and from 0% to 12% for the 60-minute treatment group.

5.2 Pharmacokinetic Properties

Distribution

The parent compound and metabolites may be present in the plasma either free or protein bound.

Metabolism

Acetylcysteine is the N-acetyl derivative of the naturally occurring amino acid, L-cysteine, and is deacetylated in the liver to cysteine, or oxidised to other metabolites such as N-acetylcystine or N,N-diacetylcystine.

Excretion

Following intravenous administration, mean terminal half lives have been calculated to be 1.95 and 5.58 hours respectively for reduced and total acetylcysteine. Renal clearance accounts for about 30% of total body clearance.

5.3 Preclinical Safety Data

Genotoxicity

No evidence of mutagenicity was obtained in limited gene mutation assays with acetylcysteine. The potential for acetylcysteine to cause chromosomal damage has not been investigated.

Carcinogenicity

Carcinogenicity assays have not been performed with acetylcysteine. In rats, no evidence of carcinogenicity was reported following 18 months of daily dietary administration of acetylcysteine at 60% of the maximum clinical dose, on a body surface area basis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Disodium edetate

Sodium hydroxide

Water for injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special Precautions for Storage

DBL Acetylcysteine Injection Concentrate should be stored below 25°C. Protect from light.

6.5 Nature and Contents of Container

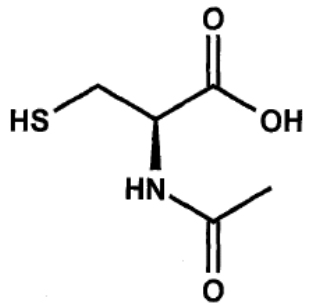
DBL Acetylcysteine Injection Concentrate is supplied in ampoules of 10 mL (acetylcysteine 200 mg/mL) for intravenous administration. It is available in packs of 10 ampoules.

6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical Properties

Chemical structure



The chemical name of acetylcysteine is (2R)-2-(acetylamino)-3-sulphanylpropanoic acid.

Molecular Formula: $C_5H_9NO_3S$

Molecular Weight: 163.2

CAS number

616-91-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

4 July 2006

10. DATE OF REVISION

1 March 2021

Summary Table of Changes

Section changed	Summary of new information
4.1	Correction of spelling error for ‘hepatotoxicity’
4.2	Revision of dosing regimen in accordance to updated guidelines on paracetamol poisoning
4.4	Addition of cautionary text on paediatric use Addition of clinical data information on paediatric use
4.6	Statement regarding animal studies.
5.1	Addition of Observational study - Paediatric patients & Safety study